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One-Pot Three Steps Synthesis of Cerpegin

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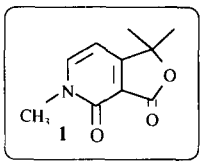
Abstract: Cerpegin **1** was synthesized in a one-pot reaction at room temperature catalysed by cesium carbonate with an overall of 75% yield. 3-Hydroxy-3-methyl-2-butanone **2** reacted with diethyl malonate **3** to give 2-ethoxycarbonyl-3,4,4-trimethyl-2-buten-4-olide **4**. Then **4** with s-triazine gave to 1,1-dimethylfuro[3,4-c]pyridine-3,4(1*H*, 5*H*)-dione **5** and which was alkylated with methyliodide to cerpegin . Copyright © 1996 Published by Elsevier Science Ltd

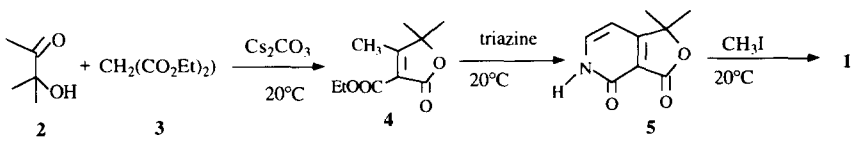
The alkaloid from *Ceropegia juncea* Roxb., cerpegin is a relatively rarely naturally occuring pyridone. Its structure was elucidated as 1,1,5-trimethylfuro[3,4-c] pyridine-3,4(1*H*, 5*H*)-dione **1**[1] *Ceropegia juncea* is reported to be a tranquillising, anti-inflammatory, analgesic and antiulcer Indian plant[2].



Four syntheses of cerpegin have been reported in the literature[3], employing three to six synthetic steps with sophisticated reaction conditions (low temperature of -78°C, use of lithium reagents) in relatively low total yields of 28%, 21%, 15%, and 34% respectively.

All the above synthesis are difficult to adapt to the synthesis of cerpegin analogues in pharmaceutical research. Because of the novelty of its structure and our continuing interest in furanone synthesis[4], we undertook the synthesis of **1**. Avetisyan *et al* have synthesized α,β-unsaturated γ-lactones by condensation of 3-hydroxy-3-methyl-2-butanone **2** with malonate esters using EtONa as catalyst in ethanol[5]. Balogh *et al.* have also reported the synthesis of pyridone ring in ethyl 4-substituted 2-methyl-5-oxo-5,6-naphthyridine-3-carboxylates from pyridinedicarboxylates and s-triazine using EtONa[6]. The key steps in our synthesis are the preparation of 2-ethoxycarbonyl-3,4,4-trimethyl-2-buten-4-olide **4** by Knoevenagel reaction of **2** with **3**, and the preparation of pyridone 1,1-dimethylfuro[3,4-c]pyridine-3,4(1*H*, 5*H*)-dione **5** from s-triazine and 2-ethoxycarbonyl-3,4,4-trimethyl-2-buten-4-olide **4**.

Scheme 1: One-pot synthesis of Cerpegin **1**



The product **4** (yield 85%) was obtained from 3-hydroxy-3-methyl-2-butanone **2** (1eq.) and diethyl

malonate **3** (1eq.) employing Cs_2CO_3 (2eq.) at room temperature using phase transfer catalysis (PTC) with Aliquat 336 as a catalyst . The reaction of **4** with s-triazine in the presence of EtONa in ethanol led to the pyridone **5** with a yield of 90%. These results and the fact that **4** can be alkylated [3a] with CH_3I in presence of Na_2CO_3 stimulate us to perform a one-pot synthesis of **1** using Cs_2CO_3 as a base. We report herein a very efficient and convenient one-pot route to cerpegin from commercially available **2**, **3**, Cs_2CO_3, s-triazine and MeI at room temperature with catalyst Cs_2CO_3 (scheme 1)[7]. All reactions take place in basic media (Cs_2CO_3+Aliquat) under PTC conditions and lead to cerpegin in a one-pot reaction without separating the intermediates. The overall yield of this one-pot synthesis is 75%.

This easy and convenient one-pot synthesis provides an example of efficient route to furo[3,4-c] pyridine-3,4 (1 *H*, 5 *H*)-dione and provides a potential route to the cerpegin analogues.

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7. In a round-bottomed flask, **4** (1 mmol), **5** (1 mmol), Aliquat 336 (0.012 g) EtOH (0.5 ml) and Cs_2CO_3 (2.5 mmol) were added and then the mixture was stirred at room temperature (r.t.) for 40 min. to give **3**. S-triazine (1 mmol) was added to the mixture, and the reaction mixture was stirred for 60 min. before the addition of CH_3I (16 mmol, 1 ml). After stirring at r.t. for 15 hours the reaction mixture was separated on a silica gel column. The products were eluted with CH_2Cl_2-EtOH/CH_2Cl_2 and gave cerpegin **1** [0.75 mmol., 145 mg (75% total yield)]. The product was obtained as pale yellow needles (CH_2Cl_2-EtOH). Mp 267-270°C(lit.[1] 268-270°C); IR (KBr, cm^{-1}): 1752 (C=O, lactone), 1666 (C-O), 1598, 1552, 1080; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.59 (6 H, s, 2 x CH_3), 3.64 (3 H, s, N-CH_3), 6.27 (1 H, d, *J* = 6.7 Hz, CC<u>H</u>=CHN), 7.68 (1 H, d, *J* =6.7 Hz, CCH=C<u>H</u>N); ^{13}C-NMR (62 MHz, $CDCl_3$) δ 171.93, 166.87, 157.89, 145.96, 112.17, 98.38, 82.51, 37.75 (N-CH_3), 26.05 (2 x Me). MS (70eV) m/z : 193 [M+·] (34.58), 178 [M-CH_3]$^+$ (100), 150 [M-CH_3CO]$^+$ (4.79), 136 (3.65), 108 (12.87), 79 (5.79), 42 (49.67).

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